

# Development of Nickel-on-Charcoal as a “Dirt-Cheap” Heterogeneous Catalyst: A Personal Account

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Received March 1, 2001; Accepted March 9, 2001

**Abstract:** A personal account tracing the origins and continuing evolution of nickel-on-charcoal (Ni/C) as a practical, alternative, group 10 metal catalyst is presented. Discussed are applications to several “name reactions” which lead to both carbon–carbon and carbon–nitrogen bond constructions utilizing inexpensive aryl chlorides as substrates. Reductions of chloroarenes are also catalyzed by Ni/C, a process which may be worthy of consideration in terms of environmental clean-up of PCBs and dioxins. Collaborative efforts are also mentioned aimed at probing the surface structure of Ni/C, with the goal of enhancing catalyst activity. Future directions for development of heterogeneous nickel catalysts are proposed.

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## 1 Introduction: Nickel-on-Charcoal? Never Heard of It ...

The talk I had just given at Hoffmann-La Roche in Basel in April of 1996 was over, during which our lat-

est unpublished work on syntheses of coenzyme Q<sup>[1]</sup> and vitamins K<sub>1</sub> and K<sub>2</sub><sup>[2]</sup> was revealed for the first time (Scheme 1). Whether the chemistry was viewed as competitive with their routes<sup>[3]</sup> to either target was not discussed; in fact, there was very little post-seminar

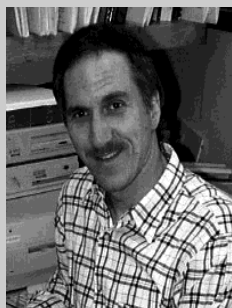
exchange. Since the key coupling step between a polyprenoidal side-chain and a chloromethylated *para*-quinone is mediated by Ni(0) *in solution*,<sup>[2,4]</sup> I volunteered the comment that we had plans to look into using such a catalyst mounted on a solid support.

After naming a few possibilities, one member of the audience, seemingly nonchalantly, suggested charcoal as an alternative. Although I was pleased to accept an honorarium at the end of the day, this off-the-cuff remark would not soon be forgotten. Indeed, it was a long 12-hour plane ride back to California, which in a (luckily) upgraded-to-business class seat provided plenty of peace and quiet during which “Ni/C” could be seriously contemplated.

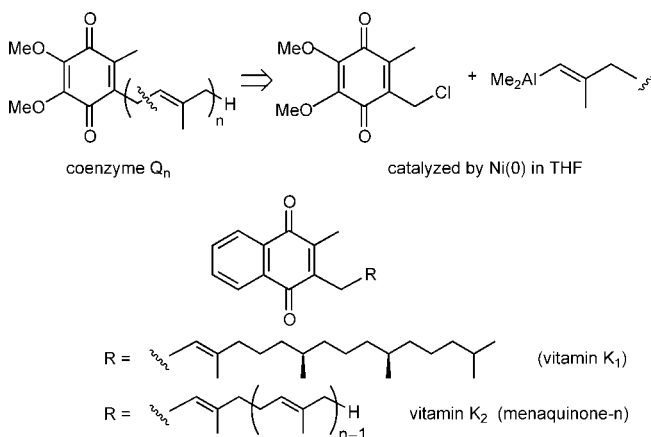
The notion of placing nickel on charcoal had an immediate appeal to me. Although it was clear that the popularity of Ni(0) as a catalyst in *solution* for effecting C–C bond formation was rapidly increasing,<sup>[5]</sup> and even more recently found to be effective for the construction of carbon–heteroatom bonds,<sup>[6]</sup> competitive heterogeneous catalysis with nickel might to some degree counter concerns over the issue of toxicity regardless of the percentage of catalyst involved. Both Ni(II) salts and charcoal are certainly inexpensive, and if capable of mediating chemistry normally reserved for palladium,<sup>[7]</sup> in principle Ni/C might find

**Keywords:** aromatic aminations; aryl chlorides; biaryls; cross-couplings; heterogeneous catalysis; nickel-on-charcoal

**Bruce Lipshutz**, born in New York City in late 1951, pursued undergraduate work at SUNY Binghamton, being introduced to organic chemistry by Howard Alper with whom his first research experience was gained. Graduate work with Harry Wasserman at Yale led to his Ph.D., after which postdoctoral studies were conducted as an ACS Fellow with E. J. Corey at Harvard. His independent academic career began in 1979 as an Assistant Professor at UC Santa Barbara, where he is now Professor of Chemistry. Research in his group has been directed toward the development of new reagents and synthetic methodology that are useful and practical. Much the work places an accent on organometallics, in particular involving Cu-, Ni-, and Pd-catalyzed processes. Applications to natural products total, or partial, syntheses which highlight the new chemistry contributed represent an important component of the group's efforts.



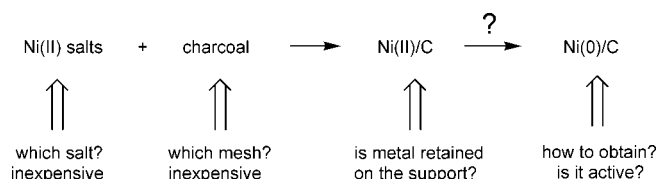
its way into the arsenal of synthetic reagents (Scheme 2). As a bonus, one might anticipate the usually more reactive nickel(0) undergoing coupling<sup>[8]</sup> with less reactive aryl chlorides<sup>[9]</sup> as partners. Secondly, charcoal-supported Ni(0) should greatly simplify workup *via* filtration of this heterogeneous 'dirt' away from the desired product(s) remaining in solution.<sup>[10]</sup>



**Scheme 1.** Key disconnection for double bond stereocontrol en route to CoQ and vitamins  $K_1$  and  $K_2$ .

Thus, while the virtues of Ni/C were far from cryptic, it was quickly appreciated that what we had in hand was little more than scribbles at 33,000 feet. I cer-

tainly had no experience in heterogeneous catalysis, and while some of the more prominent solid supports were available for equal consideration (e.g., silica,<sup>[11a]</sup> alumina,<sup>[11b]</sup> clay,<sup>[11c]</sup> polystyrene resin,<sup>[11d,11e]</sup> dendrimers,<sup>[11f]</sup> etc.), it was hard to argue against the large surface area and small cost factors inherent to charcoal. It was, therefore, more than obvious that working on this project was going to be a learning experience from the ground up. The key to success, as is so often the case, would be to place this assignment in the hands of a graduate student having the wherewithal to transform paper chemistry into reality.



**Scheme 2.** Practical considerations in developing a nickel-on-charcoal catalyst.

Enter Peter Blomgren. This east coast transplant from Rutgers, arriving in the fall of 1997, was the result of two former Corey group connections working in my favor. As an undergraduate at Rutgers, Peter was recommended to me by Spencer Knapp, to whose bench at Harvard I was assigned upon his departure in 1977. Secondly, Peter just happened to spend over a year doing research in medicinal chemistry at Bristol-Myers Squibb in Princeton, a group run by David Floyd (my former labmate at Harvard). It took no time for Peter to see the challenges before us and, already the wiser with industrial experience to his credit, to evaluate the risk-to-reward proportionality. From my standpoint, although risky, placing this project squarely in Peter's hands just seemed 'right'.

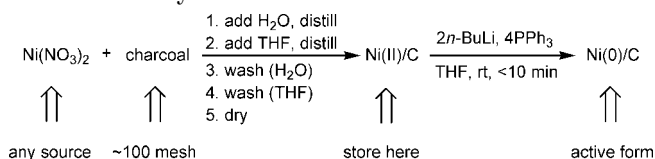
## 2 Mixing a Ni(II) Salt with Charcoal: Getting It to 'Stick' and Reduction to Ni(0)

So Peter went to the library and started digging. We thought an understanding of how Pd/C is made would provide insight, but instead, extensive information on several metals impregnated onto charcoal was uncovered.<sup>[12]</sup> It seems that many groups spanning physical and analytical chemistry, as well as surface science, had made claims to having prepared Ni/C years ago, but under what circumstances? Virtually all prior work called for preparing "Ni(II)/C" by mixing a nickel(II) salt in water with activated charcoal followed by evaporation of solvent. Subsequent heating under a variety of gaseous atmospheres (e.g.,  $H_2$ ,  $N_2$ , or air) led to the corresponding reduced species

“Ni(0)/C”, which has been used in reactions with numerous *gaseous* substrates.<sup>[12–14]</sup>

This background information was not, to put it mildly, “reassuring” as to whether (1) nickel, in either oxidation state, would stay adsorbed on the solid support to be used in an *organic* medium, and (2) the derived “Ni(0)/C”, arrived at via heating of the Ni(II) precursor, would be active and well-behaved toward aromatic chlorides and various organometallic coupling partners. Nonetheless, these papers did direct our attention toward the likelihood that nickel *nitrate* would be the salt of choice for mounting and retaining Ni(II) on charcoal, a phenomenon attributed to a lower aggregation state of Ni(NO<sub>3</sub>)<sub>2</sub>, as opposed to, e.g., nickel chloride, at the drying stage.<sup>[14]</sup> The importance of this lead cannot be overstated, for it was of paramount concern that we establish almost immediately that the nickel, once on charcoal, stays there. We were certainly not interested in a solid support that simply supplied a slow bleed of metal only to effect catalysis in solution.

Peter’s recipe for Ni(II)/C would also need to be simple and reproducible, for otherwise its use could ultimately open a Pandora’s box of future problems, not to mention the prospects for e-mail from frustrated researchers unable to repeat our work. Thus, by modifying a literature route, and using Ni(NO<sub>3</sub>)<sub>2</sub>,<sup>[14]</sup> the initial stage of generating nickel(II)-on-charcoal was relatively straightforward. The charcoal was readily slurried in water, to which was then added an aqueous solution of the Ni(II) salt, followed by distillation of the water and THF washings at atmospheric pressure to thereby afford Ni(II)/C (Scheme 3). Subsequent drying of the charcoal under vacuum at 100 °C removes most of the water of crystallization. Excessive heating of the dried material, however, was likely to significantly erode eventual catalyst activity<sup>[13a,15]</sup> and, hence, another means of generating a zero-valent species might well have to be developed. Of the many commercially available charcoals, we looked for one that would (a) lead to, and maintain, relatively high loadings of nickel; (b) be inexpensive; (c) afford reproducible results, and (d) of course, be catalytically active for the desired cross-couplings with various organometallic reagents. Several sources of charcoal (e.g., from wood, coconuts, etc.) were tested, with the high surface area characterizing either Darco KB-B-100 or KB-100 mesh carbon (from wood, both sold by Aldrich, catalog #27810-6 and 27-809-2, respectively), ultimately leading to an active Ni/C catalyst.



**Scheme 3.** Sequence of operations for preparing catalytically active Ni/C.

## General Procedure for the Preparation of Ni(II)/C

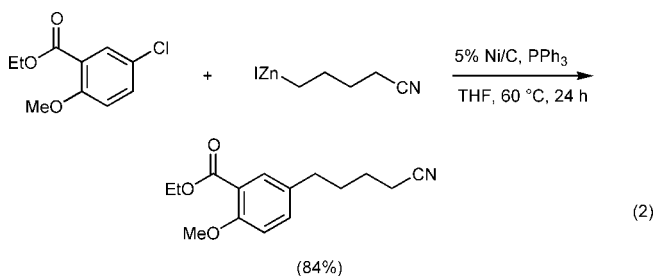
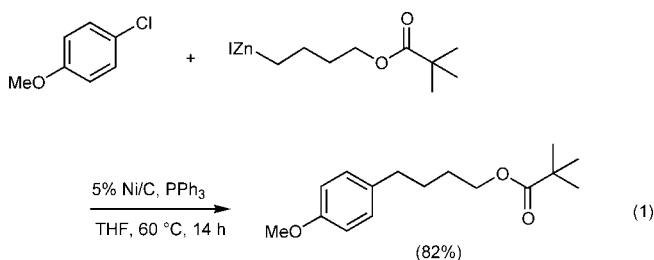
Darco® activated carbon [KB-B-100 mesh, iron < 100 ppm, surface area 1600 m<sup>2</sup>/g (dry basis), pore volume ~2 cm<sup>3</sup>/g (dry basis)] (10.0 g, including 25% H<sub>2</sub>O), Ni(NO<sub>3</sub>)<sub>2</sub> · 6H<sub>2</sub>O (1.64 g, 5.6 mmol), and degassed H<sub>2</sub>O (200 mL) were added to a 250 mL round-bottomed flask charged with a magnetic stirring bar. The mixture was heated in a sand bath equilibrated at 170 °C and the water was allowed to distill under an atmosphere of argon until dry. The sand bath was then cooled and *undistilled*, degassed THF (100 mL) was introduced and the mixture was placed in the sand bath equilibrated at 100 °C. The liquid was again permitted to distill under a positive argon flow. The black solid was then washed with degassed H<sub>2</sub>O (2 × 100 mL), distilled THF (2 × 50 mL), and dried under vacuum (0.5 mm Hg) at 100 °C for 12 h. Evaporation of the filtrates and determination of the nickel content by difference in weight led to a level of 0.64 mmol/g catalyst.

Once the Ni(II) had been mounted, we next tackled its conversion to the active zero oxidation state. Known is the possibility for simply heating Ni(II)/C to >400 °C in an oil or sand bath,<sup>[15]</sup> which drives off H<sub>2</sub>O and oxides of nitrogen in addition to effecting the reduction. More practical is the addition of between two and four equivalents of *n*-BuLi per nickel, done in THF at ambient temperatures, together with (empirically-derived) four equivalents of PPh<sub>3</sub>, which effects the reduction in minutes. That such an approach was likely to be successful rested on the analogous reduction reported by Miyaoura in 1996 on a nickel(II) salt [NiCl<sub>2</sub>(DPPF)].<sup>[17]</sup> Also of note is Negishi’s protocol using *n*-BuLi to reduce PdCl<sub>2</sub>, which had appeared a decade earlier.<sup>[18]</sup> Thus, we chose to simply ignore the heterogeneous state of the ingredients in the flask, and hope that if reduction did take place that the Ni(0) remained on the charcoal. A particularly encouraging sign at this point was that the settled mixture showed no hint of red color to the THF solution. Had it been otherwise, this color would have been a sure indication that Ni(PPh<sub>3</sub>)<sub>4</sub> was present and that our fledgling program in heterogeneous catalysis was not likely to progress. Ongoing controversy in the literature regarding this issue (i.e., leaching of the catalyst) involving Pd/C was also not viewed by us as “encouraging”.<sup>[19]</sup>

## 3 First Results: Negishi-Like Couplings with Functionalized Zinc Reagents

Since the presumed active Ni(0)/C had been generated in THF, we decided to initially disclose the reagent as a catalyst for mediating Negishi-like couplings<sup>[20]</sup> of organozinc halides with aryl chlorides.<sup>[21]</sup> Hence, when Peter took a THF slurry of active 5% Ni(0)/C along with 20% PPh<sub>3</sub>, introduced the aryl

chloride followed by the alkylzinc iodide and refluxed the mixture for 12–24 hours, an efficient reaction was indicated by TLC. The catalyst appears to work equally well for electron-rich aryl chlorides (Equation 1) as with substrates bearing electron-withdrawing groups, or cases containing both types of substituents (Equation 2). Upon completion of the coupling, a simple filtration away from the Ni/C followed by solvent removal *in vacuo* suffices to leave the crude material ready for further purification. Thus, elimination of a typical aqueous reaction workup highlights the savings in time and materials offered, in general, by such heterogeneous processes.<sup>[10]</sup> Attempts at using lesser amounts of phosphine had a surprisingly deleterious effect on the extent of conversion, a phenomenon left at the time for future investigation.



### Representative Procedure for Ni/C-Catalyzed Negishi Couplings of a Functionalized Organozinc Iodide with an Aryl Chloride

Equation 1:<sup>[21]</sup> To a flame-dried, 25-mL round-bottom flask was added Ni(II)/C (136 mg, 0.05 mmol, 0.37 mmol/g catalyst) and triphenylphosphine (53 mg, 0.20 mmol) under argon at room temperature. Dry THF (1.8 mL) was added and the slurry allowed to stir for 20 min. *n*-Butyllithium (38  $\mu$ L, 2.6 M in hexanes, 0.10 mmol) was added dropwise with stirring. After 5 min, 4-chloroanisole (143 mg, 1.0 mmol) was added. Upon cooling the mixture to  $-78^{\circ}\text{C}$ , the iodozinc reagent [prepared from iodobutyl pivaloate (568 mg, 2.0 mmol) and zinc dust (144 mg, 2.2 mmol) in 2.0 mL THF] containing lithium chloride (85 mg, 2.0 mmol) was then slowly added via a cannula. The mixture was warmed to rt over 0.5 h, and finally heated at reflux for 12–24 h. The mixture was then filtered through a pad of Celite and the filter cake further washed with THF (30 mL). Solvents were then removed on a rotary evaporator and the resulting oily residue chromatographed on silica gel, producing 217 mg

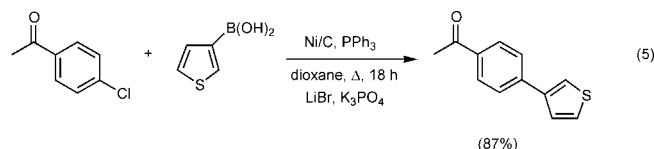
(82%) of the desired product as a clear oil;  $R_f$  = 0.25 (hexanes/ethyl acetate, 20/1).

Although it did not take long for Peter to establish generality to this new methodology, we were still awaiting the arrival of “Murphy”, whose Laws rarely fail to keep any sense of unbridled enthusiasm for new discoveries well in check. The major hurdle left to overcome, which could totally derail this project, was the establishment of true heterogeneous catalysis, preferably evaluated in a quantitative fashion. The state-of-the-art method for obtaining such information was spelled “ICP” (i.e., “inductively coupled plasma” spectroscopy, a form of atomic emission spectroscopy),<sup>[22]</sup> a very powerful and sensitive method of analysis. Sooner or later, we had to know: How much nickel comes off the charcoal during the reaction? With assistance by staff in the Materials Department, where the instrument is housed, Peter went about quantifying residual Ni in solution after filtration of the Ni/C followed by the usual digestion of the residue with *aqua regia*. It was a tense moment to put it mildly, but the data were unequivocal. Of the 0.05 equivalents Ni by weight relative to substrate mounted on charcoal, at most 4% had been lost during a Negishi coupling. Some runs showed lower percentages, but in the worst case scenario, we were seeing [(5%)  $\times$  (4%)] or 0.002 equivalents of nickel in solution relative to aryl chloride. Although we both put stock in these data, as experimentalists, there were control reactions that had to be ‘N Sync’ with the ICP results. Most telling were two experiments: (1) stopping a Ni/C-catalyzed Negishi coupling prematurely; for example, at the *ca.* 30% level of conversion, filtering off the catalyst and re-exposing the *solution* to the reaction conditions, led to no additional product formation; and (2) using the ICP datum of a 4% loss of nickel from the 0.05 equivalents Ni/C used, a THF solution containing 0.002 equivalents Ni(PPh<sub>3</sub>)<sub>4</sub> versus substrate was prepared and used with the same coupling partners. The result: no substitution product was formed according to capillary GC analysis of the crude reaction mixture.

## 4 Is Ni/C Compatible with Grignard Reagents? Kumada-Like Couplings

At this point, things were looking good; real good. Since a new graduate student, Takashi Tomioka (nicknamed ‘Tak’ by the group) had just arrived from Nagoya University, I immediately assigned him the job of studying Kumada couplings<sup>[23]</sup> mediated by our new friend, Ni/C. My ulterior motive, at the time kept strictly confidential, was to see if Ni(0)/C could be reproduced not only by a new pair of hands, but

by the hands of a first year student. Tak quickly gained the reputation of being the hardest working student in the group (quite an accolade from his peers), and thus within a few months time, notwithstanding his courses, cumulative exams, and teaching obligations, he turned out a dozen examples of Ni/C-catalyzed Grignard couplings with aryl chlorides.<sup>[24]</sup> Grignards of many 'flavors' (i.e., alkyl, aryl, and benzylic) could be used with equal success (Equation 3). Lurking in the background, however, as Peter had been forced to confront, was the ICP experiment to determine the extent of catalyst bleed. Tak was unphased by this threat, perhaps buoyed by the benefits of precedent in his favor, in spite of the fact that Grignards would be the most reactive organometallic to which Ni/C would be exposed. Well, as Tak and Peter headed over to the ICP spectrometer, volumetrics in hand, I waited, seemingly forever. Finally, Tak came in with his numbers, which revealed that only 2.68% nickel (i.e., 0.0013 equivalents *vs.* substrate) had been found in solution associated with these Kumada-like couplings.

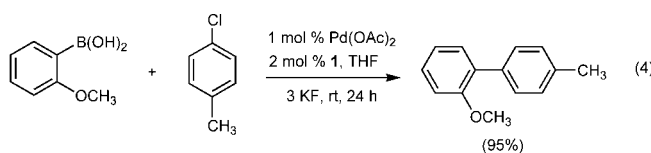


### Representative Procedure for Ni/C-Catalyzed Kumada Couplings of a Grignard Reagent with an Aryl Chloride

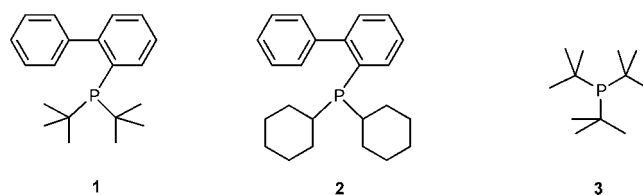
Equation 3:<sup>[24]</sup> To a flame-dried, 15-mL round-bottomed flask at room temperature were added Ni(II)/C (86 mg, 0.05 mmol, 0.58 mmol/g catalyst), triphenylphosphine (52 mg, 0.20 mmol), and anhydrous lithium bromide (87 mg, 1.0 mmol), all under an inert atmosphere. Dry THF (1 mL) was added *via* syringe and the slurry allowed to stir for 20 min. *n*-Butyllithium (40  $\mu$ L, 2.47 M in hexane, 0.10 mmol) was added to the heterogeneous mixture at room temperature and the mixture stirred for 20 min. *tert*-Butyl-(4-chlorobenzoyloxy)dimethylsilane (257 mg, 1.0 mmol) was then added dropwise with stirring. After cooling the mixture to  $-78^{\circ}\text{C}$ , 4-methoxybenzylmagnesium chloride (2.5 mL, 0.57 M in THF, 1.4 mmol) was added slowly. The mixture was warmed to rt over 0.5 h, and finally heated to reflux for 9 h. Ethanol (5 mL) was then added and the slurry stirred so as to quench excess Grignard reagent. The crude mixture was filtered through filter paper and the filter cake further washed with ethanol and THF. Solvents were then removed on a rotary evaporator and the crude mixture treated with 30%  $\text{H}_2\text{O}_2$  in order to form  $\text{Ph}_3\text{PO}$  which facilitated separation by column chromatography<sup>[17]</sup> on silica gel, eluting with 5% EtOAc/hexanes to produce 274.3 mg (80%) of a colorless oil.

## 5 Suzuki Couplings with Aryl Chlorides: Ni/C Takes the Challenge

The *News*, however, caught me off-guard. That is, in *Chemical & Engineering News*, a series of articles (usually scribed by Stephen Stinson)<sup>[25]</sup> which began in June of 1998 was focusing neither on Negishi nor Kumada couplings. What was attracting considerable attention were the impressive advances being made by those working on Suzuki couplings between aryl chlorides and boronic acids.<sup>[26]</sup> Highlighted were commercial availability and stability of aryl chlorides, along with the attractive shelf life of boronic acids and their environmentally innocuous borate by-products. New phosphines (e. g., **1**, **2**, and **3**, Figure 1) which enable reaction temperatures as low as  $25^{\circ}\text{C}$  in several cases were also featured prominently (Equation 4), as were those which allow for couplings to be run under aqueous conditions.<sup>[26c]</sup> Accepting my error in having misread the times, I finally decided after noting yet another report on this subject in this magazine that if the world wants Suzuki couplings, we were going to respond... but with different chemistry. That is, rather than involving palladium(0) in solution, we would endeavor to develop heterogeneous conditions using Ni/C. I needed to pick a student who would work long and hard to bring these popular couplings into the realm of Ni/C-catalyzed processes. After receiving an e-mail note from Peter's labmate Joe Sclafani, thereby reminding me of his address which began labrat@..., I knew immediately to whom this assignment was heading.

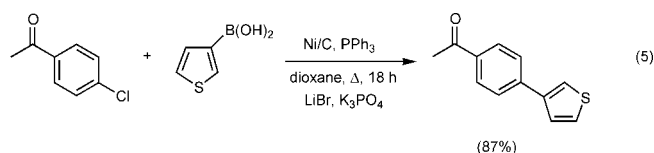


Joe, an easy going 'paesano' from Philly, PA, who kept a large goldfish tank right next to his hood which he jokingly justified as an indicator of toxic substances that might be escaping, gladly accepted this challenge. We faced many an impasse along the way, but with sheer effort by Joe in the lab, unexpected pro-



**Figure 1.** Highly effective ligands for Pd-catalyzed Suzuki couplings.

blems were eventually remedied. For example, there was a tendency noted toward greater amounts of aryl chloride homocoupling than we had seen in previous Ni/C-catalyzed reactions. Fortunately, inclusion of excess LiBr in the pot reduced this side reaction to a tolerable level (*ca.* 5%). After Joe had put some nice examples in our Table,<sup>[27]</sup> which included functionalized reaction partners (Equation 5), it was clear that we were on a roll ... or so I thought.

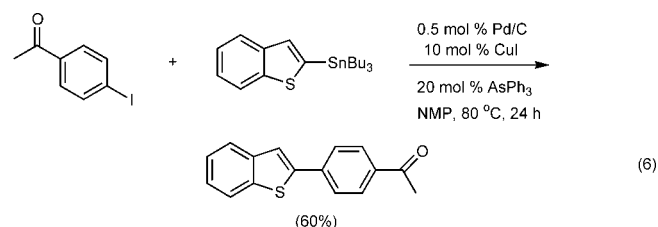


### General Procedure for Suzuki Couplings Catalyzed by Ni/C

Equation 5:<sup>[27]</sup> In a 10-mL, round-bottomed flask under an inert atmosphere of argon were combined triphenylphosphine (75 mg, 0.28 mmol, 0.4 equiv), and Ni(II)/C (106 mg, 0.07 mmol, 0.1 equiv, 0.66 mmol/g catalyst). Dioxane (2.5 mL) was added *via* syringe and the mixture allowed to stir for 20 min. In a second flask were combined K<sub>3</sub>PO<sub>4</sub> (547 mg, 2.58 mmol, 3.6 equiv), LiBr (150 mg, 1.73 mmol), 3-thiophenylboronic acid (138 mg, 1.08 mmol, 1.5 equiv), and 4-chloroacetophenone (95  $\mu$ L, 0.72 mmol). To the flask containing the Ni/C mixture was introduced dropwise *n*-butyllithium (2.55 M, 120  $\mu$ L, 0.28 mmol, 0.4 equiv) to form the active Ni(0)/C complex. The charcoal mixture was allowed to stir for 5 min and the flask was placed in a salted ice slush bath until frozen. The contents of the second flask were added to the frozen mixture and the flask was fitted with an argon purged condenser. The mixture was allowed to melt and then placed in a sand bath preheated to 135 °C, where it was refluxed for 18 h. Upon cooling, the mixture was poured onto a fritted funnel containing a pad of Celite and washed with methanol (40 mL). The filtrate was collected and adsorbed onto silica gel, and then subjected to column chromatography. The product eluted with 10% EtOAc/hexanes and was isolated as a white solid (127 mg, 87%).

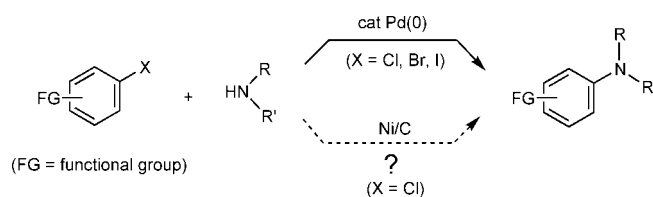
Notwithstanding publication of this latest group effort in *Tetrahedron* as a contribution to Ken Nicholas' *Symposium-in-Print* on organometallics in synthesis,<sup>[28]</sup> it seemed that few in the community knew about this work, at least judging from several subsequent conversations I had at various industrial labs. It was reasoned that further deployment for purposes of effecting additional 'name reactions' within the organopalladium sphere of influence (e.g., Stille, Heck, Sonogashira, etc.)<sup>[7]</sup> would not necessarily do anything to help promote Ni/C as a viable alternative catalyst. Moreover, Pd/C was already "on the market", with several reports indicating that it can be very effective and convenient in mediating Negishi,<sup>[29]</sup> Stille<sup>[30]</sup> (e.g., Equation 6; *cf.* procedure below),<sup>[30a]</sup>

Suzuki,<sup>[31]</sup> and Heck-type couplings,<sup>[32]</sup> as well as other carbon-carbon and carbon-heteroatom bond formations (e.g., symmetrical biaryls,<sup>[33a]</sup> and allylic aminations,<sup>[11b,33b]</sup> respectively). What might raise an eyebrow or two, however, would be an application to the 'hot' chemistry of aromatic aminations.<sup>[34]</sup> That is, could Ni/C serve as an alternative to Pd(0)-mediated couplings between aryl halides and primary or secondary amines *en route* to anilines (Scheme 4), precursors to a multitude of heterocycles of interest to pharmaceutical firms, as well as to material scientists (e.g., polyanilines)?<sup>[35]</sup> Intuitively, Ni/C should mediate C-N bond constructions, but I knew that to believe our conditions for C-C bond-forming processes would simply translate to heteroatom substitutions was a bit of a 'stretch', to put it mildly.



### Typical Experimental Procedure for a Stille Coupling Catalyzed by Pd/C: 2-(4-Acetylphenyl)benzothiophene

Equation 6:<sup>[30a]</sup> A solution consisting of *N*-methyl-2-pyrrolidinone (5 mL), 4-iodoacetophenone (121 mg, 0.5 mmol), triphenylarsine (30 mg, 0.1 mmol), and CuI (10 mg, 0.05 mmol) was degassed by sparging with nitrogen. 2-Tributylstannylthiophene (310 mg, 0.7 mmol) was added by syringe and the reaction was placed in an oil bath set at 80 °C. Under positive nitrogen pressure, Pd/C (10%, 3 mg, 0.003 mmol) was added and the mixture was allowed to stir at 80 °C for 24 h. The reaction was cooled, treated with a saturated KF solution and allowed to stir for 30 min. The mixture was passed through a pad of Celite and rinsed with ether. The filtrate was washed with water, then dried (MgSO<sub>4</sub>) and concentrated to give a crude yellow solid. Chromatography (10% ethyl acetate/hexanes) on silica gel furnished the desired product as white flakes (74 mg, 60%); mp 207–208 °C.



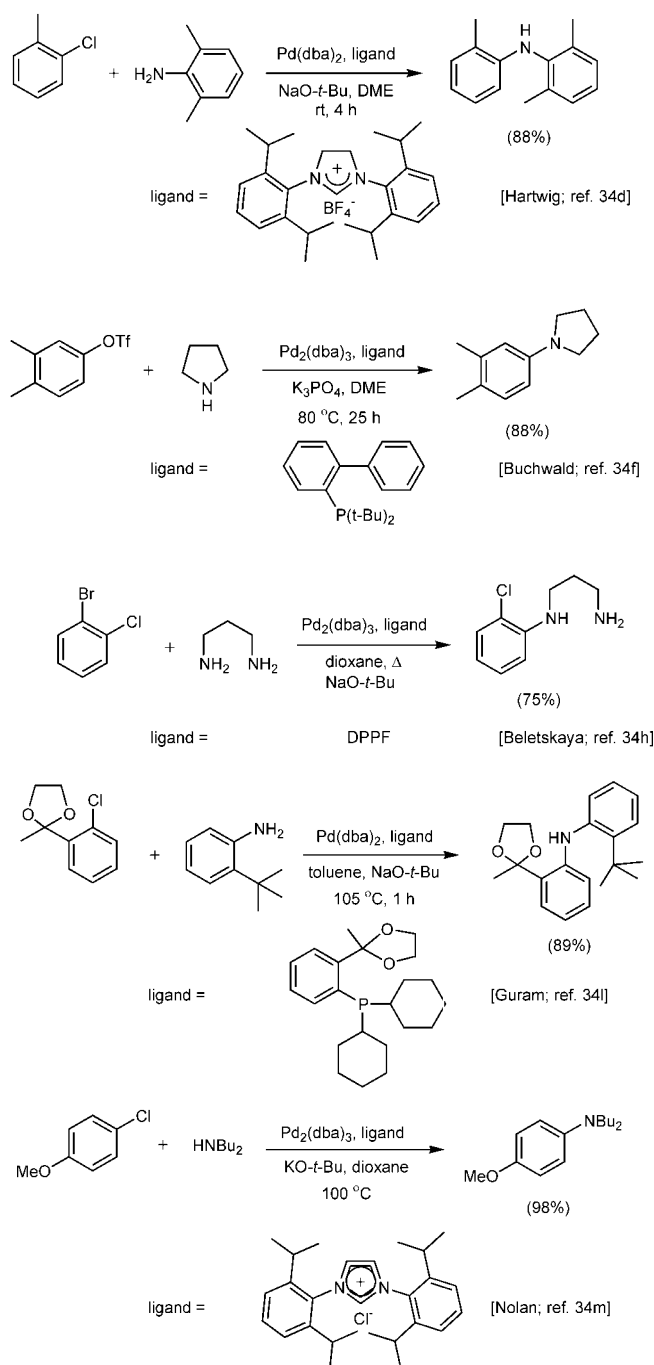
**Scheme 4.** Anticipated application of Ni/C to aromatic amination reactions.

## 6 Aminations of Aryl Chlorides: and the ‘Magic’ Phosphine Ligand is...

Some luck, however, was in the cards, as an old acquaintance at Sumitomo Chemical Co., Dr. Shinji Nishii, had arranged to send a co-worker, Mr. Hiroshi Ueda, to our labs for a two year stint. ‘Hiro’ was immediately asked to consider venturing into this unknown area. The project seemed like a good match in that he would hopefully be developing new chemistry that Sumitomo, among other companies, might actually opt to use someday, and he would become their ‘in house’ expert. But would a group 10 divalent metal impregnated on charcoal embrace basic nitrogen and cleanly extrude the reductively coupled product?

Hiro quickly cleared the initial bar, generating a stash of fresh Ni(II)/C under argon that remained on call. The amination chemistry reported at that time<sup>[54]</sup> provided foreshadowing of the trials and tribulations that were in our future. Most of our apprehension stemmed from the subtleties that were apparent with respect to the role of ligands in the corresponding Pd(0)-catalyzed events in solution. Leading work from the Hartwig<sup>[34a–34d]</sup> and Buchwald<sup>[34e–34g]</sup> schools, supported as well by several additional studies by other groups on this theme,<sup>[34h–34p]</sup> taught us that the difference between success and failure would likely lie with this reaction variable (Scheme 5). Moreover, conditions favorable toward Pd-catalyzed couplings in solution, or even those mediated by catalytic Ni(COD)<sub>2</sub> in hot toluene,<sup>[56]</sup> might bear little resemblance to those potentially driven by nickel mounted on a solid support about which I freely admitted we knew essentially nothing.

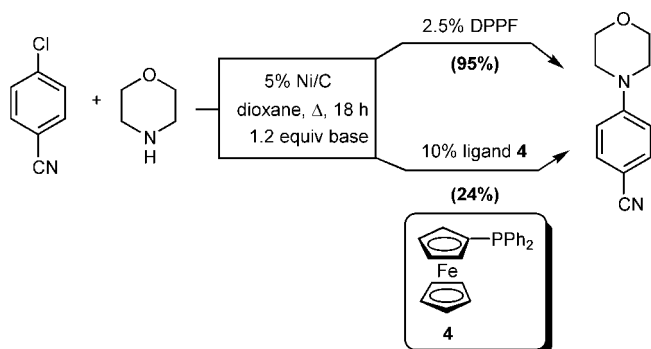
My apprehension, unfortunately, was fully justified in time. With every phosphine ligand Hiro tried in attempts to make a simple aniline derivative, including trials with DPPF,<sup>[37]</sup> under conditions used so successfully by Beletskaya [on diamine couplings with Pd<sub>2</sub>(dba)<sub>3</sub>; cf. Scheme 5]<sup>[54h]</sup> and by Buchwald [on aryl aminations using nickel(0) in solution],<sup>[56]</sup> every GC analysis led to the exact same yield for each reaction: zilch, nada, zip, donuts. In short, we never saw any aniline product. True, we were not anticipating PPh<sub>3</sub> to do the job here, as previously it so willingly had, but apparently neither could several other common phosphine or amine ligands, whether mono- or bidentate in nature [Cy<sub>3</sub>P, P(*o*-tol)<sub>5</sub>, dppe, dppp, DPPF, 1,10-phenanthroline,<sup>[36]</sup> etc.]. In hearing this continuous stream of negative news, I couldn’t help but ask Hiro: “Whazzzzzaahhh with these reactions?” After all, we were not looking to ‘tweak’ conditions to enhance initially obtained modest yields; we’re talkin’ zero here. But Hiro persevered. He moved down his list of reaction variables; diligently, methodically, pa-



**Scheme 5.** Ligand variations in representative Pd-catalyzed aminations.

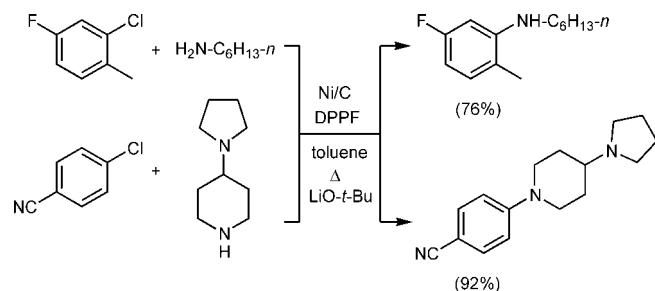
tiently. Rather than toluene as solvent, along with commonly used DPPF<sup>[54h,55]</sup> and NaO-*t*-Bu, the switch to dioxane gave us our first indication of a limited coupling. Further optimization quickly revealed the importance of utilizing higher substrate concentrations (>0.7 M) as well as LiO-*t*-Bu as the base. Remarkably, however, only in the presence of DPPF did any coupling occur whatsoever. In returning to toluene, where there may be greater solubility of this

base than in dioxane, we were rewarded with a GC trace that was indicative of a highly efficient process. Finally, Hiro had discovered that “spike” in an all but flat baseline that described our level of success over several months. Although back in business, we both knew all along that when the ‘magic’ ligand was found we would have no clue as to why, or how, it controls these couplings. Indeed, an attempt employing up to 10 mole percent of Kagan’s monophosphine version of DPPF, (diphenylphosphino)ferrocene, **4**,<sup>[58]</sup> under otherwise identical conditions used in our test case, led to only 24% conversion (Scheme 6).



**Scheme 6.** Comparison of DPPF and (diphenylphosphino)ferrocene, **4**.

Focusing on the particulars of this amination provided us with additional observations that continued to contrast with both our earlier work with Ni/C, as well as much of the existing Pd(0)-based literature on this transformation.<sup>[54]</sup> For example, while C–C couplings with Ni/C required 3–4 equivalents of PPh<sub>3</sub> per loading of nickel,<sup>[20,23,26]</sup> 0.5 equivalents of DPPF sufficed for aminations. Hence, our ‘standard’ conditions ultimately became 5% Ni/C, 2.5% DPPF, and 1.2 equivalents of LiO-*t*-Bu in refluxing toluene. Important was the finding that loss of nickel from the charcoal was minimal, on the order of only 0.0015 equivalents (versus substrate), again strongly suggestive of chemistry occurring on the solid support. It was a long trek, and while our survey of aryl chlorides and amines indicates elements of merit and competitive efficiency associated with use of this catalyst (Scheme 7), the method is certainly not without limitations. For example, displacement of chloride by an aza-crown ether<sup>[58]</sup> unfortunately led to no reaction. Identical outcomes were also observed with imidazole,<sup>[40]</sup> hexamethyldisilazane, and the sta base.<sup>[41]</sup> Nonetheless, it is the first reasonably general protocol for effecting aryl aminations under heterogeneous conditions, not to mention the rather favorable economic aspects to Ni/C.<sup>[42]</sup> Somehow, even before its disclosure, Steve Stinson knew about it, asking for details on the catalyst to assist with his write-up, although this has yet to appear.



**Scheme 7.** Representative Ni/C-catalyzed aminations of aryl chlorides.

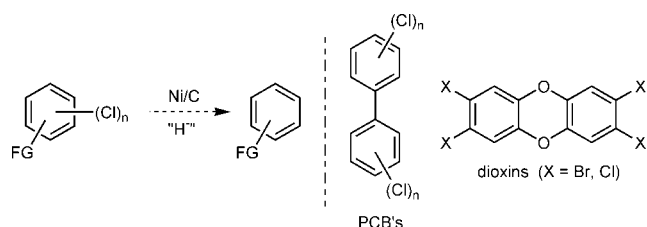
### Representative Procedure for the Amination of Aryl Chlorides

Scheme 7:<sup>[42]</sup> Ni(II)/C (58.2 mg, 0.038 mmol, 0.05 equiv, 0.64 mmol/g catalyst), DPPF (10.7 mg, 0.019 mmol), and lithium *tert*-butoxide (74.3 mg, 0.90 mmol) were added to a flame-dried, 5-mL round-bottomed flask under a blanket of argon at room temperature. Dry toluene (0.40 mL) was added by syringe and the slurry allowed to stir for 40 min. *n*-Butyllithium (33  $\mu$ L, 2.30 M in hexanes, 0.075 mmol) was added dropwise with stirring. After 20 min, 4-chlorobenzonitrile (104.2 mg, 0.75 mmol) and 4-(1-pyrrolidinyl)piperidine (244 mg, 1.5 mmol) which were dissolved in dry toluene (0.60 mL) were added, followed by heating to reflux for 3 h (the oil bath temperature was set to 130 °C). After cooling to room temperature, the crude reaction mixture was then filtered through a sintered glass filter containing a layer of Celite, and the filter cake was further washed with methanol and dichloromethane. The filtrate was collected, solvents were removed on a rotary evaporator, and the crude product was then purified by flash chromatography on neutral alumina with ethyl acetate/methanol (1:1) to give 175.9 mg (0.69 mmol; 92%) of the product as a tan solid.

## 7 Reductive Dechlorinations of Aryl Chlorides: Searching for a Mild Source of Hydride

So where to go with this chemistry now? We decided to briefly test the waters in the reduction manifold. That is, can Ni/C be used to convert an aromatic C–Cl bond to the corresponding C–H, and do so, in particular, in molecules bearing extensive functionality (Scheme 8, left)? From the standpoint of fine chemicals synthesis, many physiologically active natural products<sup>[45]</sup> contain such bonds (e.g., vancomycin),<sup>[44]</sup> and one avenue to establishing structure–activity relationships is to remove this halogen. From the environmental perspective, such reductions might be considered as an inexpensive means of depleting existing stockpiles of PCBs and dioxins (Scheme 8, right).<sup>[45]</sup> Lastly, the strong aryl C–Cl bond could be viewed as both a protecting group as well as a transient *ortho-para* director for electrophilic substitution.

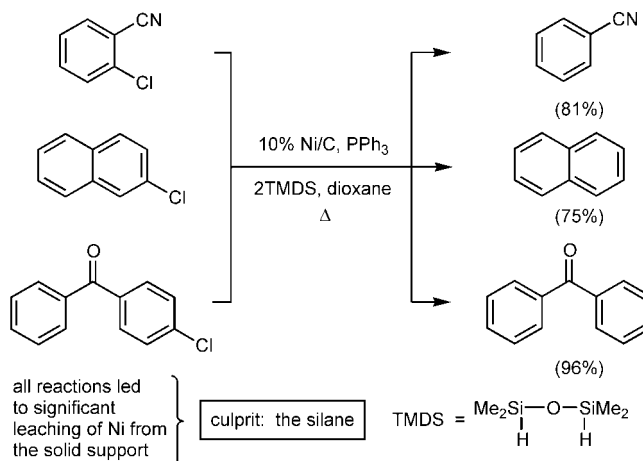




**Scheme 8.** Potential use of inexpensive Ni/C in reductions of aryl chlorides including PCBs and dioxins.

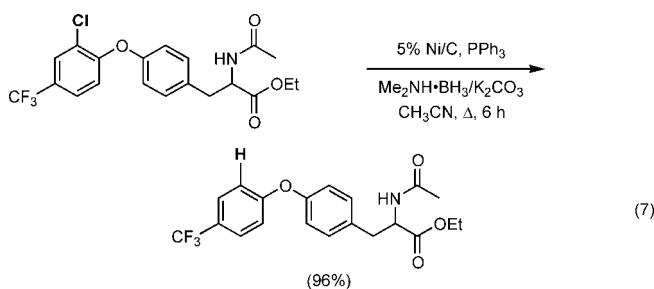
Initially, Mr. Kimihiko Sato, on loan for a summer from Tamotsu Takahashi's group at Hokkaido University, started the search for reduction conditions. We knew that this would be a tough exercise in finding a mild source of hydride ("H<sup>+</sup>" in Scheme 8) that while unreactive toward most functional groups (FG), in particular those containing electrophilic centers, would be capable of displacing chloride ion from a presumed Ni(II) center. Here, yet again, we were "treated" to another surprise concerning Ni/C. Kimi's early results suggested that both Red-Al and NaBH<sub>4</sub> would effect the desired chemistry, but these would not be the answer to the fine chemicals side of the story. Although Tak's main project involved a synthesis of the non-racemic biaryl portion of vancomycin,<sup>[43]</sup> he too had a list of reducing agents to be screened. He first tested H<sub>2</sub> at atmospheric pressure to no avail. Our ongoing program in catalytic copper hydride chemistry,<sup>[46]</sup> which has gained us much appreciation for the chemistry of several inexpensive silanes [such as TMDS (tetramethyldisiloxane)<sup>[47]</sup> and PMHS (polymethylhydrosiloxane)],<sup>[48,49]</sup> strongly encouraged trials with one of these quite mild sources of H<sup>+</sup>. Remarkably, Ni/C together with TMDS in refluxing THF led to very efficient reductive dechlorination (Scheme 9). Just about every functional group tested (including a ketone, but *not* an aldehyde) was untouched under these conditions. As we were close to considering this problem solved, I felt an uneasiness about this study; it was just *too* easy, too good to be true. The quantitative GC data from reactions of several aryl chlorides, on the other hand, were irrefutable. I can vividly recall that sense of incredulity when Tak showed me his numbers from the ICP experiments on these reactions. Although Ni/C had withstood numerous organometallics and amines, exposure of this catalyst to a silane had caused 80% of the nickel to "un-impregnate" itself from the charcoal! After Tak had completed the obligatory control experiments wherein Ni/C was treated with less reactive Et<sub>3</sub>SiH in the *absence* of substrate partners (which gave similar results), there was no denying the data. Somehow, these relatively benign silanes (unlike Grignards, organozinc halides, boronic acids, or

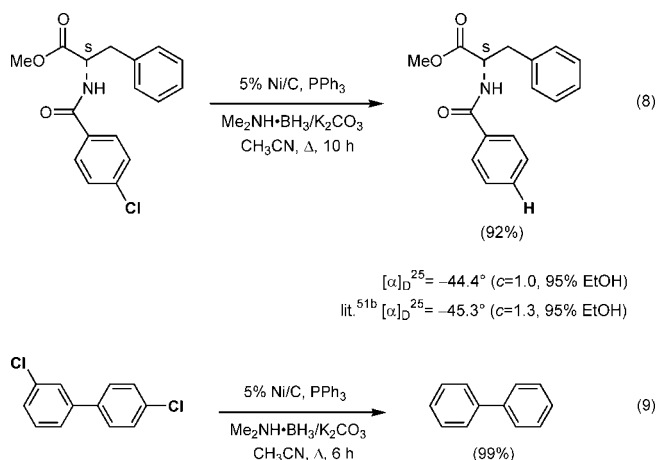
amines) have the ability to essentially wipe the charcoal surface clean of nickel. Go figure!



**Scheme 9.** Silane-mediated reductions catalyzed by Ni/C, but with leaching of the catalyst.

So Kimi and Tak kept looking for a truly mild source of hydride, which seemed at the time as scarce as electricity in California. Finally, Kimi found one that showed promise, located oddly enough in our own 'backyard': Me<sub>2</sub>NH·BH<sub>3</sub>.<sup>[50]</sup> Agreed, this is not a reagent on the tip of every synthetic chemist's tongue, but we tried it admixed 1:1 with K<sub>2</sub>CO<sub>3</sub> only to discover that it works well in the current context. Indeed, this combination, which presumably forms the kated form of the amide (i.e., Me<sub>2</sub>N-BH<sub>3</sub>K) yet bears no Lewis acidic component (i.e., K<sup>+</sup> rather than Li<sup>+</sup>),<sup>[51]</sup> is extremely effective. Chemoselectivity is good, as esters and nitriles are unaffected, and relatively acidic indole NH residues do not affect catalyst activity while the aryl carbon-chlorine bond is reduced virtually quantitatively (e.g., Equation 7). No erosion of stereochemical integrity was observed in a non-racemic secondary peptide derivative (Equation 8),<sup>[52a,52b]</sup> and the extent of loss of nickel according to the ICP data appears to be minimal (= 0.0015 equivalents in solution). Unfortunately, however, aldehydes and ketones are susceptible to reduction, and under the conditions of refluxing CH<sub>3</sub>CN, olefins are reduced (via hydroboration) as well. PCB's, on the other hand, can be reduced using Me<sub>2</sub>NH·BH<sub>3</sub>/K<sub>2</sub>CO<sub>3</sub> in high yields (Equation 9).





### Representative Procedure for the Ni/C-Catalyzed Reduction of Aryl Chlorides

Equation 7:<sup>[52a]</sup> To a flame-dried, 10-mL round-bottomed flask at room temperature were added Ni(II)/C (77.6 mg, 0.05 mmol, 0.64 mmol/g catalyst), triphenylphosphine (39 mg, 0.15 mmol), 98% dimethylamine–borane complex (66 mg, 1.1 mmol), and potassium carbonate (152 mg, 1.1 mmol), all under an argon atmosphere. Dry, deoxygenated acetonitrile (2 mL) was added via syringe and the slurry allowed to stir for 2 h. The aryl chloride (1.0 mmol, 429 mg) was added with stirring and the mixture was then heated to reflux in a 100 °C sand bath for 6 h. The crude mixture was filtered through filter paper and the filter cake further washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue purified on a silica gel column eluting with hexane–EtOAc (1:1) to afford the product as white crystals (380.7 mg, 96%).

A very practical, lingering question to which I still could not provide an answer when routinely asked about this catalyst, is whether it can be recycled. To this point, no one in the group had actually reclaimed it after filtration and simply put it back into the flask with fresh reagents to see what it would do. One day, Tak did it. It seems that Ni/C, at least from the standpoint of aryl C–Cl reductions, can be reused without loss of efficiency whatsoever (Table 1). Tak repeated the cycle three times, and in each case, the yield was >95%. We have not yet carried out similar studies for

**Table 1.** Recycling of Ni/C.

Experiment	Yield (% by GC)
1	95
2	97
3	99

either the corresponding C–C or C–N bond-forming cases, although such experiments we speculate are likely to be successful.

## 8 What Does “Ni/C” Really Look Like? Surface Science to the Rescue

Even prior to the latest study on aryl C–Cl bond reductions, we knew that the time had come to investigate the “black box”, Ni/C. What is this species that effects these varied types of displacements on aryl chlorides, but has an increasing library of idiosyncrasies that are unfolding by chance with each use? It was also intuitive that we had not developed by sheer luck the most reactive form of this catalyst possible, and that by looking in the right directions we might be able to devise a newer, more effective version of Ni/C. Along with this fundamental question of substance, ancillary issues might also be addressed, such as the critical role played by the nature and quantities of phosphine ligands present. Where within Ni/C are the phosphines situated? Why, for example, if one mixes Ni/C with four equivalents of PPh<sub>3</sub> in THF and then filters off the catalyst, do roughly two equivalents ‘stick’ to the Ni/C? If one accepts this stoichiometry, then why does the Ni/C + 2PPh<sub>3</sub> combination in any of our C–C bond-forming processes (*vide supra*)<sup>[21,24,27]</sup> seemingly never go to completion, requiring the presence of at least 3–4 equivalents of PPh<sub>3</sub> in order to ultimately realize good yields of products?

To just begin to answer some of these questions, we needed help... big time. I knew there are those out there who could tackle these problems, but these guys are usually materials scientists, not synthetic organic chemists. The techniques used to examine surfaces on which metals are positioned are completely different from those for which I was trained. Even the language is almost completely new; should we go from thought processes focused on stereo-, regio-, and chemo- descriptors to TEMs, SEMs, and STMs?<sup>[53]</sup> We had no choice. Although I was unable to recruit such co-workers here on campus, a trip to Germany was imminent during which a visit to a longtime friend (Manfred Reetz) in Mülheim was planned. My colleague Bill Kaska advised me to look for collaborators at this world-renowned Max Planck Institute (MPI), for located there is not only the best of equipment, but a number of talented and highly experienced scientists one of whom might be interested. When I arrived at the Institute and was given my schedule for the day, it was obvious that my timing, in fact, could not have been worse. Of the two people who oversee the electron microscopy facility at this Institute, Dr. Bernd Tesche was out of town,

and his associate, Mr. Bernd Spliethoff, was out ill on this day! OK, ... plan B.

The person to whom this aspect of the Ni/C project was to be given, Stefan Tasler, was not yet in Santa Barbara. He was finishing his Ph.D. in Würzburg with the world's leading authority on tetrahydroisoquinoline-containing natural products,<sup>[54]</sup> Gerhard Bringmann,<sup>[55]</sup> with whose group we share common interests in the michellamines and associated subunits (the korupensamines).<sup>[56]</sup> Having spent his graduate years intimately involved with biaryl-containing natural products that possess an element of atropisomerism,<sup>[57]</sup> Stefan indicated that he was looking for new challenges outside of the non-racemic biaryl area. He saw the problems we were facing in further developing our Ni/C chemistry, and agreed to take over this project upon arrival. Of course, he had no way of knowing that I was going to ask him to get involved long before the ink on his diploma was dry. Würzburg was not exactly a stone's throw from Mülheim, but perhaps Stefan could represent our hopes for establishing a collaboration with those at this Institute.

So Stefan traveled to Mülheim, packing a sample of our Ni(II)/C, as well as the commercial charcoal support right out of the bottle. I had informed Manfred Reetz, the Director of the Institute, about our intentions, who was most agreeable and left the decision and level of involvement to Dr. Tesche. This was a very generous offer, considering that the Reetz group, in part, is very concerned with the development of nanostructured nickel and nickel/palladium clusters,<sup>[58]</sup> aimed in part at providing quite unique heterogeneous group 10 metal catalysts.<sup>[59]</sup> Not long after the samples were brought to the MPI, a package arrived in my mailbox, thick with TEM and SEM images describing the precursor impregnated nickel(II) on this highly irregular surface. To see the potential here for getting the sorts of surface information that might lead us to a far better catalyst was quite fascinating and rather exhilarating. Based on these initial results, and with the lines of communication open, Stefan, now in Santa Barbara, discussed with Dr. Tesche and Mr. Spliethoff the next, even more exciting step: to look at the surface after the Ni(II) had been reduced to active Ni(0)/C *via* another organometallic species. This, to our knowledge, would be an unprecedented experiment. Does the reduction process using *n*-BuLi, rather than heat, alter particle size and distribution?<sup>[15]</sup> The TEM data that came from the MPI clearly pointed to the importance of just how the Ni(II)/C is activated. Using the known thermal process (i.e., heating to > 400 °C under H<sub>2</sub>),<sup>[13]</sup> particles that were mainly in the 5–15 nm range were observed, with some as large as 50 nm. Reduction of Ni(II)/C using *n*-BuLi, however, led to particles that were 2–3 nm in size, and were highly dispersed.<sup>[60]</sup>

In addition to our connection with the Mülheim

group, we happened to also hear about the Institute of Analytical & Environmental Chemistry at Martin-Luther-University in Halle (Germany), where Dr. Wolfgang Moerke, associated with Prof. Dr. Helmut Muller, is conducting related experiments. Again through Stefan's contact, a collaboration was established. Using ferromagnetic resonance (FMR) measurements on Ni(II)/C reduced by hydrogen at elevated temperatures, large particles have been observed,<sup>[61]</sup> in line with the Mülheim data.

In the course of preparing samples for our collaborators abroad, Stefan initially repeated the group's original procedure developed by Peter and reproduced with minor alterations by Joe, Tak, and Hiro. While relatively straightforward (*vide supra*), there was room for further simplifications and improvements. These efforts have just recently led to a revised protocol which offers several advantages over the original prescription in terms of both extent of handling and cost (see the Update in this issue).<sup>[62]</sup> The Ni/C generated in this modified fashion has been tested by Stefan in preliminary Kumada and Suzuki couplings, and as well by Tak in his aryl chloride reductions. The results are gratifyingly comparable, even though Stefan is now back to making biaryls!

## 9 Summary... and a Look Ahead

Considering the rich history behind the noble metal-containing catalyst Pd/C, a reagent still especially valued for its ability to effect hydrogenations of C–C multiple bonds, the absence of any body of synthetic organic chemistry based on Ni/C, in hindsight, might seem odd and perhaps, even striking. Such realizations, however, occasionally present opportunities in synthetic and, in this case, surface chemistry, which together could provide both timely and useful new technologies. Rather than applying Ni/C to related alkene and/or alkyne reductions, we have chosen to develop it as a mediator of net substitution reactions on aryl chlorides, resulting in carbon–carbon, carbon–nitrogen, and carbon–hydrogen bonds. Scattered reports on such couplings with Pd/C, in fact, pre-date the advent of Ni/C for such purposes. However, as many practitioners have noted in carrying out Pd/C-catalyzed hydrogenations, consistency from batch to batch and supplier to supplier can vary widely, which may also be a factor to consider with this alternative heterogeneous catalyst. Since Ni/C is prepared from its basic ingredients following a standardized protocol, it may prove to be of greater reproducibility across a spectrum of bond-forming events. At this point in time, however, there are many questions about our “standardized” procedure which remain to be addressed. For example, how much of the water of crystallization is actually removed from the nickel ni-

trate during the drying process? Are there any other sources of Ni(II) salts which might ultimately afford a 'hotter' catalyst? Insofar as cost is concerned, there is likely to be little argument as to the advantages of a base metal, over a precious metal, in catalyst design. Nonetheless, perhaps some preliminary comparisons between the merits of *heterogeneous* Ni(0)/C and *homogeneous* Pd(0)-catalyzed couplings would be worthwhile, as outlined in Table 2. Of course, Ni/C does not enjoy the benefits of years of efforts by groups throughout the world. But this may change over time should Ni/C, even as it currently exists, find its way into various labs with some success. Additional features now undergoing development in our labs, and surface analyses in those of our collaborators, may also be combined with future studies by others, thereby providing further catalyst improvements. In fact, even as this review as originally commissioned by the Executive Editor, Joe Richmond, and journal Editor Ryoji Noyori (both former Corey

group members) is being concluded, Stefan is having success in preparing and using nickel-on-graphite. Graphite? How would we even write such a new species over the arrow? Ni/C<sub>g</sub>?<sup>[65]</sup> Although we know even less about this 3rd generation species, it seems safe to speculate that this highly ordered, comparably inexpensive solid support holds surprises in store for us of a different nature than those already observed with relatively ill-defined charcoal. Hey, is anybody in the group already thinking buckyballs ("Ni/C<sub>60</sub>")?

The author is indebted to the UCSB students, and our collaborators in Germany, whose names appear in the text for their efforts which have resulted in the continuing evolution of nickel-on-charcoal as a viable catalyst. Both the NIH and NSF are warmly acknowledged for the continued support of our programs in heterogeneous catalysis, as is the DAAD for a postdoctoral fellowship to ST, and to the Sumitomo Company for support of HU.

**Table 2.** Ni(0)/C: Features and critical comparison with Pd(0) in solution.

Derivation	The catalyst is prepared from readily available Ni(NO <sub>3</sub> ) <sub>2</sub> and charcoal of ~100 mesh. Unlike most sources of Pd(0), it is not commercially available.
Cost	Both precursors to Ni/C are very inexpensive relative to Pd(II) or Pd(0).
Ligands	All C–C bond forming reactions examined to date with Ni/C can be effected using PPh <sub>3</sub> (usually 3–4 equiv/Ni) to ligate the catalyst. Aminations require DPPF, albeit in far lesser quantities (0.5 equiv relative to Ni). Many more variations in ligands have been utilized in Pd-mediated couplings, and their roles in several couplings are well understood.
Functional Group Compatibility	Within limitations imposed by the organometallic reaction partner, most electrophilic centers can be tolerated; several still remain to be examined. Pd(0) is likely to be more accommodating.
Efficiency	In most cases studied to date, the efficiency of Ni/C usually is reflected by the extent of conversion. When reactions go to completion, isolated yields tend to be high. Results using Pd(0) can be as good, or better.
Catalyst Re-use	Although tested in only one reaction type thus far (i. e. aromatic chloride reductions), there was no loss in effectiveness of re-isolated Ni/C after three consecutive uses. Pd(0) in solution is much tougher to reclaim.
Lifetime	When Ni(II)/C is stored carefully under Ar, this precursor to active Ni(0)/C can last for months. Stabilities of Pd(II) salts and Pd(0) sources vary widely. <sup>[64]</sup>
Usage	State of Pd-catalyzed coupling is far more advanced relative to that of Ni/C. Much lower levels of Pd(0) can usually be employed relative to Ni; however, the cost differential and the likelihood of Ni/C recycling may compensate for these differences in reactivity. Ease of workup favors Ni/C. Use of inexpensive phosphines in Ni/C-catalyzed couplings is an advantage.
Bottom line	Ni/C may be most appropriate for selected preparative scale couplings.

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